Natural Product Synthesis

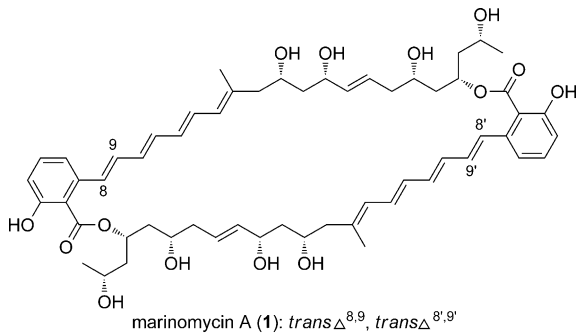
DOI: 10.1002/ange.201404408

Total Synthesis of Marinomycin A Based on a Direct Dimerization Strategy**

*Tatsuya Nishimaru, Masashi Kondo, Kimito Takeshita, Keisuke Takahashi, Jun Ishihara, and Susumi Hatakeyama**

Abstract: *The asymmetric total synthesis of (+)-marinomycin A, a 44-membered macrodiolide antitumor agent and antibiotic isolated from a marine actinomycete, Marinispora strain CNQ-140, is reported. The key features of the synthesis include the highly convergent stereocontrolled construction of the monomeric hydroxy salicylate starting from asymmetric epoxidation of the σ-symmetrical dialkenyl carbinol, and an unprecedented direct dimerization through NaHMDS-promoted double transesterification.*

In 2006, Fenical et al. disclosed the isolation of marinomycins A–C (**1**–**3**), structurally novel 44-membered C_2-symmetrical dimeric polyene-polyol macrolides, from the saline culture broth of a marine actinomycete, *Marinispora* strain CNQ-140, which was cultured from a sediment sample collected deep off the coast of La Jolla in California (Figure 1).[1]



marinomycin A (**1**): *trans*$\triangle^{8,9}$, *trans*$\triangle^{8',9'}$
marinomycin B (**2**): *cis* $\triangle^{8,9}$, *cis* $\triangle^{8',9'}$
marinomycin C (**3**): *trans*$\triangle^{8,9}$, *cis*$\triangle^{8',9'}$

Figure 1. Marinomycins A, B, and C.

These natural products exhibit potent antibiotic activity ($MIC_{90} = 0.1$–0.6 μM) against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecium* (VREF), and inhibit cancer cell proliferation in the National Cancer Institute's 60 cell-line panel ($LC_{50} = 0.2$–2.7 μM) with excellent selectivity against six of the eight melanoma cell lines.[1] It has been shown that marinomycin A (**1**) is the most potent and the presumed true natural product, which photochemically isomerizes to marinomycins B (**2**) and C (**3**).[1,2] The significant biological properties and structural challenges have made the marinomycins attractive targets for synthesis, and the total synthesis of **1** has been accomplished by Nicolaou et al.,[2] followed by Evans et al.[3] Furthermore, the synthesis of the monomeric counterpart of **1** was reported by Cossy et al.[4] Herein we report a novel convergent asymmetric total synthesis of (+)-marinomycin A (**1**) that makes use, for the first time, of a direct dimerization methodology for the construction of its 44-membered macrodiolide skeleton.

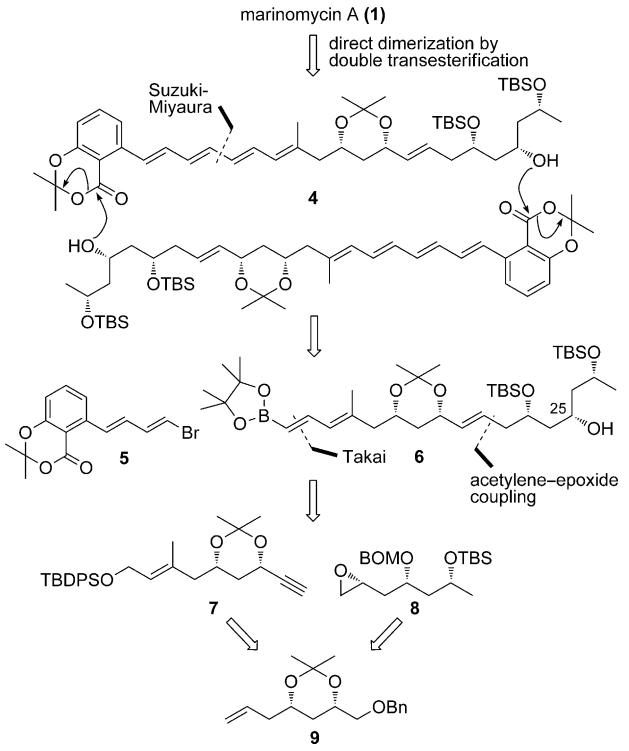
Given the C_2-symmetrical dimeric macrodiolide structure, one of the most attractive and efficient approaches is the direct dimerization of a monomeric hydroxy salicylate through using the benzo[1,3]dioxinone functionality (salicylic acid acetonide) as an active ester[3,5] in a double transesterification reaction (Scheme 1). However, it is a formidable challenge to realize this desired dimerization mode as opposed to the competitive intramolecular lactonization, which gives the corresponding 22-membered macrolide, or intermolecular oligomerization.[6] In this context, we expected that the judicious selection of appropriate protecting groups would make the conformation of a monomeric hydroxy ester ideal for the direct dimerization. In light of the conformational benefit arising from a dioxane protecting group for the macrodiolide formation as suggested by Evans et al.,[3] we temporarily selected compound **4** as the monomeric precursor since this compound seemed to be conformationally favorable for dimerization over intramolecular macrolactonization.[7] We envisioned that compound **4** could be prepared by Suzuki–Miyaura coupling[8] of the known aromatic fragment **5**[2] and boronate fragment **6**. Fragment **6** was considered to be accessible from alkyne **7** and epoxide **8** through an acetylene–epoxide coupling,[9] inversion of the C25 stereochemistry, and Takai olefination.[10] Both alkyne **7** and epoxide **8** would in turn be derived from the readily available 1,3-diol chiral building block **9** through a method we have previously developed.[11]

The synthesis of alkyne **7** commenced with the four-step preparation of enantiopure acetonide **9** from σ-symmetrical dialkenyl carbinol **10** in a sequence involving a Katsuki–Sharpless asymmetric epoxidation,[12] Mitsunobu inversion, Red-Al reduction of an epoxy alcohol with concomitant loss of a benzyloxy group as in **14**, and acetonide formation,

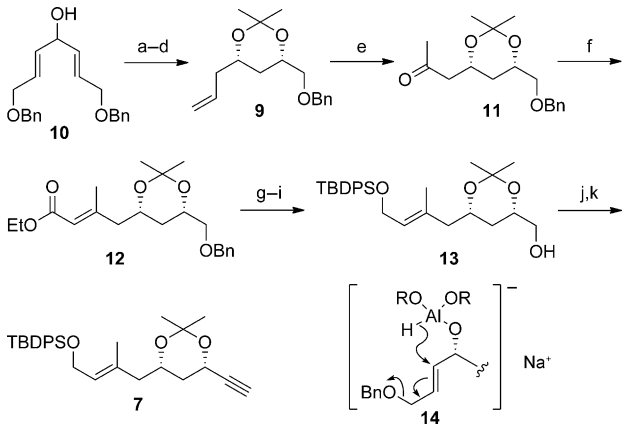
[*] T. Nishimaru, M. Kondo, K. Takeshita, Dr. K. Takahashi, Dr. J. Ishihara, Prof. Dr. S. Hatakeyama
Graduate School of Biomedical Sciences, Nagasaki University
1-14 Bunkyo-machi, Nagasaki 852-8521 (Japan)
E-mail: susumi@nagsaki-u.ac.jp

[**] This work was supported by the Grant-in-Aid (25253002) from JSPS and the Grant-in-Aid for Scientific Research on Innovative Areas "Advanced Molecular Transformations by Organocatalysis" (No. 2304) (24105526) from MEXT.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201404408.



Scheme 1. A retrosynthetic analysis of **1**. TBS = *tert*-butyldimethylsilyl, BOM = benzyloxymethyl, TBDPS = *tert*-butyldiphenylsilyl, Bn = benzyl.

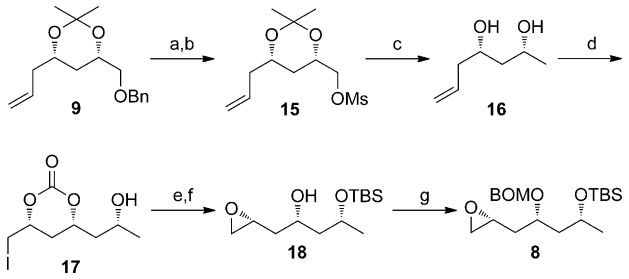


Scheme 2. Reagents and conditions: a) $Ti(OiPr)_4$ (10 mol%), D-DIPT (14 mol%), 4 Å MS, TBHP, CH_2Cl_2, −25 °C, 98% (99% *ee*); b) DEAD, PPh_3, *p*-nitrobenzoic acid, toluene, −30 °C then K_2CO_3, MeOH, 74%; c) Red-Al, toluene, 0 °C to reflux, 82%; d) 2,2-dimethoxypropane, PPTS, acetone, 99%; e) $PdCl_2$ (10 mol%), CuCl, O_2, DMF/H_2O (10:1), 82%; f) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 90% (*E*/*Z* = 6:1); g) DIBAL-H, CH_2Cl_2, −78 °C, 99%; h) TBDPSCl, imidazole, DMF; i) Li, naphthalene, THF, −50 °C, 96% (2 steps); j) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C; k) $MeCOC(N_2)P(O)(OEt)_2$, K_2CO_3, MeOH, 88% (2 steps). DIPT = diisopropyl tartrate, TBHP = *tert*-butyl hydroperoxide, DEAD = diethyl azodicarboxylate, Red-Al = sodium bis(2-methoxyethoxy)aluminum hydride, PPTS = pyridinium 4-toluenesulfonate, DMF = *N*,*N*-dimethylformamide, THF = tetrahydrofuran, DIBAL-H = diisobutylaluminum hydride, DMSO = dimethyl sulfoxide, Red-Al = sodium bis(2-methoxyethoxy)aluminum hydride.

according to our established procedure[11] (Scheme 2). Wacker oxidation[13] of **9** delivered methyl ketone **11**, which was subjected to Horner–Wadsworth–Emmons olefination to afford a 6:1 mixture of *E*-ester **12**, the *Z*-isomer of which was chromatographically separated. Upon successive DIBAL-H reduction, silylation, and debenzylation[14] with lithium naphthalenide, **12** afforded alcohol **13** in excellent yield. After Swern oxidation of **13**, the resulting aldehyde was then subjected to Seyferth–Gilbert homologation by using the Ohira–Bestmann reagent[15] to provide alkyne **7**. The overall yield of **7** from **10** was 31% (11 steps).

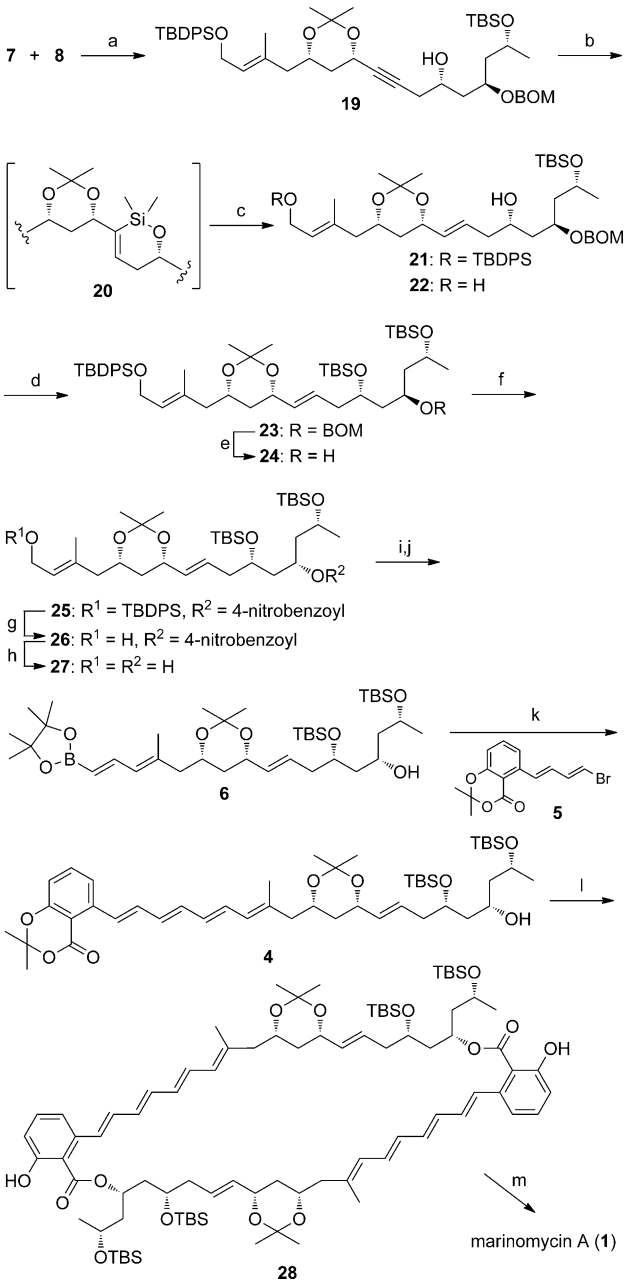
Epoxide **8** was also prepared from **9** by a highly diastereoselective seven-step transformation in 51% overall yield (Scheme 3). Reductive debenzylation of **9** followed by mesylation of the resulting alcohol gave mesylate **15** in quantitative yield. Mesylate **15** was then reduced with $LiAlH_4$ and the reaction mixture was directly acidified by the addition of aqueous HCl and MeOH to afford 1,3-diol **16** without serious loss of the initially formed volatile product. According to Cardillo's method,[16] **16** was lithiated and reacted with CO_2 followed by I_2 to provide iodocarbonate **17** as a single diastereomer in good yield. Silylation of **17** followed by methanolysis gave epoxy alcohol **18**, which was then protected as the corresponding BOM ether to provide epoxide **8**.

With the required alkyne **7** and epoxide **8** in hand, the stage was set for the preparation of monomeric hydroxy salicylate **4** starting from the union of these two fragments (Scheme 4). The lithium acetylide generated from **7** was reacted with **8** in the presence of $BF_3{\cdot}OEt_2$[9] to give homopropargyl alcohol **19** in almost quantitative yield.



Scheme 3. Reagents and conditions: a) Li, naphthalene, THF, −50 °C, 98%; b) MsCl, NEt_3, CH_2Cl_2, 99%; c) $LiAlH_4$, Et_2O, reflux, then 1 M HCl, MeOH, 84%; d) *n*BuLi, THF, −78 °C, then CO_2, I_2, 86%; e) TBSCl, imidazole, DMF, 78%; f) K_2CO_3, MeOH, 93%; g) $BnOCH_2Cl$, iPr_2NEt, CH_2Cl_2, 100%. Ms = methanesulfonyl.

Although several attempts to reduce **19** to *E*-alkene **21** by using Red-Al or $LiAlH_4$ met with failure, we found that Trost's procedure,[17] which involves silylation, intramolecular hydrosilylation, and desilylation, effected this transformation satisfactorily. Silylation of **19** with 1,1,3,3-tetramethyldisilazane followed by intramolecular hydrosilylation with $[Cp^*Ru(MeCN)_3]PF_6$ as the catalyst furnished dihydrooxasiline **20**, which was then directly subjected to AgF-mediated desilylation to afford *E*-alkene **21** and diol **22** in 52% and 34% yields, respectively. Since **22** was quantitatively converted into **21** by selective silylation, the total yield of **21** was 86%. Protection of the secondary alcohol of **21** as the corresponding TBS ether followed by removal of the BOM group of **23** by using lithium naphthalenide[14] produced



Scheme 4. Reagents and conditions: a) **7**, *n*BuLi, BF_3·Et_2O, THF, −78 °C, then **8**, −78 °C, 97%; b) 1,1,3,3-tetramethyldisilazane, then $[Cp^*Ru(MeCN)_3]PF_6$ (10 mol%), CH_2Cl_2; c) AgF, THF/MeOH/DMSO/H_2O (10:6:3:2), **21** (52%), **22** (34%); d) TBSCl, imidazole, DMF, 97%; e) Li, naphthalene, THF, −60 °C, 100%; f) DEAD, PPh_3, 4-nitrobenzoic acid, toluene/THF (1:3), 76%; g) TBAF, AcOH, DMF, 89%; h) NaOMe, THF/MeOH (1:2), 100%; i) TEMPO, $PhI(OAc)_2$, phosphate buffer (pH 7.0), MeCN, 0 °C, 97%; j) $Cl_2CHB(pin)$, $CrCl_2$, LiI, THF; k) **5**, $Pd(PPh_3)_4$ (40 mol%), 0.5 M aq KOH, THF, 25 °C, 10 min, 48% (2 steps); l) NaHMDS, THF, −10 °C, 71%; m) 3.0 M $HClO_4$/THF (1:5), 71%. TBAF = tetra-*n*-butylammonium fluoride, TEMPO = 2,2,6,6-tetramethyl-l-piperidinoxyl (free radical), HMDS = 1,1,1,3,3,3-hexamethyldisilazane.

alcohol **24** in almost quantitative yield. Mitsunobu inversion[18] of the C25 hydroxy group afforded 4-nitrobenzoate **25**, which, upon selective desilylation[19] and methanolytic removal of the 4-nitrobenzoyl group, delivered diol **27** via **26** in good yield. After TEMPO oxidation of **27**, the resulting aldehyde was directly subjected to Takai olefination with pinacol (dichloromethyl)boronate[10] to stereoselectively produce *E*-boronate **6**. Without purification, boronate **6** was then coupled to the aromatic fragment **5** under Suzuki–Miyaura reaction conditions to furnish the required monomeric hydroxy salicylate **4** in 48% overall yield from **27**.

To complete the total synthesis, we addressed the crucial direct dimerization of monomer **4** under various transesterification conditions. As shown in Table 1, when this reaction

Table 1: Base-promoted dimerization of **4**.

Entry	Method[b]	Base	Yield [%][a] of **28**	Recovered **4**
1	A	NaHMDS	30	14
2	A	KHMDS	9	45
3	A	LHMDS	6	32
4	A	LDA	6	20
5	B	NaHMDS	71	0

[a] Yield of isolated product. [b] Method A: base (2 equiv) in THF (1.0 M) was added to a THF solution of **4** (0.05 M) at −10 °C and the mixture was stirred at −10 °C for 2 min. Method B: compound **4** in THF (0.036 M) was added to NaHMDS (4 equiv) in THF (0.014 M) at −10 °C over 30 min and the mixture was stirred at −10 °C for 15 min.

was conducted by adding NaHMDS, KHMDS, LHMDS, or LDA to a THF solution of **4** at −10 °C, the production of the desired 44-membered macrodiolide **28** was observed within 2 min but the yields of isolated product were 30% at best owing to rather fast decomposition of **4** (entries 1–4).

Lowering the reaction temperature did not improve the yield of **28** at all. However, to our delight, reverse slow addition of **4** to NaHMDS in THF at −10 °C dramatically improved the dimerization reaction and **28** was isolated in 71% yield (entry 5). In this reaction, the corresponding 22-membered macrolide and oligomers were not identified. Finally, exposure of **28** to aqueous $HClO_4$ enabled the removal of all of the protecting groups to cleanly furnish marinomycin A (**1**) in 71% yield without isomerization of the labile tetraene functionality after reverse phase ODS column chromatography. The synthetic marinomycin A (**1**) exhibited spectral properties identical in all respects to those reported for the natural product.[1,3]

In conclusion, we have accomplished the convergent total synthesis of (+)-marinomycin A (**1**) in 24 steps (the longest linear sequence) in 4.0% overall yield starting from asymmetric epoxidation of σ-symmetrical dialkenyl carbinol **10**. The synthesis is practical and enables us to obtain hundred mg quantities of marinomycin A (**1**). The present work presents the first successful example of a direct dimerization approach to marinomycin A (**1**).

Received: April 17, 2014
Published online: June 24, 2014

Keywords: antibiotics · antitumor agents · macrodiolides · natural products · total synthesis

[1] H. C. Kwon, C. A. Kauffman, P. R. Jensen, W. Fenical, *J. Am. Chem. Soc.* **2006**, *128*, 1622.
[2] a) K. C. Nicolaou, A. L. Nold, R. R. Milburn, C. S. Schindler, *Angew. Chem.* **2006**, *118*, 6677; *Angew. Chem. Int. Ed.* **2006**, *45*, 6527; b) K. C. Nicolaou, A. L. Nold, R. R. Milburn, C. S. Schindler, K. P. Cole, J. Yamaguchi, *J. Am. Chem. Soc.* **2007**, *129*, 1760.
[3] P. A. Evans, M. H. Huang, J. L. Michael, S. Maroto, *Nat. Chem.* **2012**, *4*, 680.
[4] a) D. Amans, V. Bellosta, J. Cossy, *Org. Lett.* **2007**, *9*, 1453; b) D. Amans, L. Bareille, V. Bellosta, J. Cossy, *J. Org. Chem.* **2009**, *74*, 7665.
[5] For selected recent examples of transesterification of salicylic acid acetonides, see: a) J. S. S. Rountree, P. V. Murphy, *Org. Lett.* **2009**, *11*, 871; b) J. S. Yadav, N. Thrimurtulu, M. A. Rahman, J. S. Reddy, A. R. Prasad, B. V. S. Reddy, *Synthesis* **2010**, 3657; c) D. Martinez-Solorio, K. A. Belmore, M. P. Jenning, *J. Org. Chem.* **2011**, *76*, 3898; d) R. Chegondi, M. M. L. Tan, P. R. Hanson, *J. Org. Chem.* **2011**, *76*, 3909; e) K. Zhu, J. S. Panek, *Org. Lett.* **2011**, *13*, 4652; f) C. M. Schneider, K. Khownium, W. Li, J. T. Spletstoser, T. Haack, G. I. Georg, *Angew. Chem. Int. Ed.* **2011**, *50*, 7855; *Angew. Chem.* **2011**, *123*, 8001.
[6] Nicolaou et al.[2] reported that the attempted double Suzuki dimerization to form the 44-membered macrodiolide favored intramolecular cyclization to provide the 22-membered macrolide. In addition, Evans et al.[3] reported that the monomeric hydroxy salicylate with MOM protecting groups and an ethylidene acetal underwent base-mediated decomposition.
[7] Molecular mechanical calculations (MMFF*, Macro Model 8.6) suggested that the intramolecular cyclization of **4** to the 22-membered macrolide was unlikely because of the remote distance between the salicic ester carbonyl and hydroxy group (7.562 Å). On the other hand, the formation of 44-membered macrodiolide **28** from the corresponding hydroxy salicylate generated by the initial transesterification looked favorable owing to the proximity of the reaction sites (3.489 Å). See the Supporting Information.
[8] For reviews: a) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457; b) A. Suzuki, *J. Synth. Org. Chem. Jpn.* **2005**, *63*, 312.
[9] M. Yamaguchi, I. Hirao, *Tetrahedron Lett.* **1983**, *24*, 391.
[10] a) K. Takai, N. Shinomiya, H. Kaihara, N. Yoshida, T. Moriwake, K. Utimoto, *Synlett* **1995**, 963; b) K. Takai, Y. Kunisada, Y. Tachibana, N. Yamaji, E. Nakatani, *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1581.
[11] a) S. Hatakeyama, K. Satoh, S. Takano, *Tetrahedron Lett.* **1993**, *34*, 7425; b) T. Esumi, H. Hukuyama, R. Oribe, K. Kawazoe, Y. Iwabuchi, H. Irie, S. Hatakeyama, *Tetrahedron Lett.* **1997**, *38*, 4823; c) T. Nishioka, Y. Iwabuchi, H. Irie, S. Hatakeyama, *Tetrahedron Lett.* **1998**, *39*, 5597; d) T. Esumi, R. Kimura, M. Mori, Y. Iwabuchi, H. Irie, S. Hatakeyama, *Heterocycles* **2000**, *52*, 525; e) H. Masaki, J. Maeyama, K. Kamada, T. Esumi, Y. Iwabuchi, S. Hatakeyama, *J. Am. Chem. Soc.* **2000**, *122*, 5216.
[12] a) S. Hatakeyama, K. Sakurai, S. Takano, *J. Chem. Soc. Chem. Commun.* **1985**, 1759; b) V. Jäger, B. Häfele, *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 87; *Angew. Chem.* **1986**, *98*, 89; c) S. L. Schreiber, T. S. Schreibers, D. B. Smith, *J. Am. Chem. Soc.* **1987**, *109*, 1525.
[13] J. Tsuji, H. Nagashima, H. Nemoto, *Org. Synth.* **1984**, *62*, 9.
[14] H.-J. Liu, J. Yip, K.-S. Shia, *Tetrahedron Lett.* **1997**, *38*, 2253.
[15] a) S. Ohira, *Synth. Commun.* **1989**, *19*, 561; b) S. Müller, B. Liepold, G. J. Roth, H. J. Bestmann, *Synlett* **1996**, 521; c) G. j. Roth, B. Liepold, S. G. Muller, H. J. Bestmann, *Synthesis* **2004**, 59.
[16] a) G. Cardillo, M. Orena, G. Poni, S. Sandri, *J. Chem. Soc. Chem. Commun.* **1981**, 465; b) A. Bongini, G. Cardillo, M. Orena, G. Poni, S. Sandri, *J. Org. Chem.* **1982**, *47*, 4626.
[17] B. M. Trost, Z. T. Ball, *J. Am. Chem. Soc.* **2005**, *127*, 17644.
[18] S. F. Martin, J. A. Dodge, *Tetrahedron Lett.* **1991**, *32*, 3017.
[19] S. Higashibayashi, K. Shinko, T. Ishizu, K. Hashimoto, H. Shirahama, M. Nakata, *Synlett* **2000**, 1306.